



EDITORIAL

Electronic cigarettes: Tumultuous times

Key words: acute respiratory distress syndrome, e-cigarette, infection and inflammation.

'E-cigarettes will prompt young people to take up smoking. I recommend that national governments ban, or at least regulate, them'

Dr Margaret Chan-former WHO Director-General, China Daily 2015¹

In a keynote lecture at the 2017 American Thoracic Society conference, Dr Anthony S. Fauci, Head of the National Institute of Allergy and Infectious Diseases, described how he had been part of a briefing for President Trump's transitional team in late 2016. The briefing was from a range of experts and was related to civil emergencies that Trump might face during his Presidency. Having served under four previous presidents, Dr Fauci warned the team that each administration had faced at least one major infectious disease emergency—human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) West Nile virus, SARS, 2009 H1N1 influenza, Ebola and Zika virus. Less than 3 years later, it appears that Donald Trump's developing emergency is not an infectious disease but two phenomena related to electronic cigarettes (EC)—an extraordinary rise of EC use in youth² and a multistate outbreak of lung injury associated with EC product use.³

A common link in the current outbreak, if it exists, has not been determined. Diverse pathologies have been reported, as has been the case with the sporadic case reports of acute lung injury related to EC since the first use in 2012.⁴ At the time of writing, there had been nearly 1604 cases reported using the Centers for Disease Control and Prevention (CDC) case definition and 34 deaths⁵—the youngest reported in the lay media being just 17.⁶ Respiratory failure requiring ventilatory support is common. The most common imaging findings are suggestive of bronchiolitis obliterans/cryptogenic organizing pneumonia or diffuse ground-glass opacities.⁷ In the previous case reports, the course was described as favourable after cessation of EC use, but it is too early to determine the extent of residual lung injury in the current outbreak. A range of exposures are reported but, as the CDC has made clear, the investigation is ongoing.⁸ Many have used cannabis oil or cannabinoids, but whether that use was sporadic or regular is uncertain, and this exposure cannot explain all cases. Those who have publicly claimed that contaminants must be responsible ignore the geographical dispersion of cases and the spread in time of symptom onset and seem oblivious to the reality that, from the perspective of the lung, everything in an EC is a contaminant.

What is most surprising at the present time is that so many are surprised that such an outbreak might occur. The human bronchial epithelium is exposed; it is vulnerable but also resilient with innate mechanisms that are protective and also adaptive after injury. Ween *et al.* recently reported findings of a carefully conducted study on the effects of e-liquid exposure in human bronchial epithelial cells.⁹ There were three key findings. EC liquids, with a variety of constituents, induce damage that manifests as necrosis and apoptosis; macrophage efferocytosis, an adaptive mechanism that clears apoptotic cells, is compromised; and purchasers of EC liquids can have no confidence in the constituents that they are exposing their lungs to—with three versions of apple flavour having very different chemical mixes. The observations of Ween *et al.* have even greater pertinence after the report of histopathology from 17 cases within the current outbreak.¹⁰ Open biopsy findings suggest that the dominant pathology is a form of airway-based chemical pneumonitis and not exogenous lipid pneumonia as previously believed by some.

These findings complement an NIH-funded comprehensive 2017 review by Chun *et al.* on the effects of EC on the lung, which examined a combination of in vivo and in vitro studies.¹¹ Since that publication, we have also seen the seminal work of Ghosh *et al.* who observed airway inflammation in a man in vivo, describing the proteomic characteristic of bronchial tissue in smokers, EC users and controls.¹² In summary, considering significant positive and negative changes, there were 292 changes seen with smoking, of which 78 were also seen with EC use. Importantly, there were 113 separate proteomic changes that occurred only with EC use. This would not be unexpected by an open mind because the nature of the lung exposure is very different.

Youth use of EC in the United States has been described as an epidemic by the Food and Drug Administration (FDA),¹³ with this assertion further supported by the latest data from the Monitoring the Future study.² EC use in the last 30 days was 25.4% in 12th grade school students, 20.2% in 10th graders and 9.0% in 8th graders, more than doubling in 2 years for each group. Daily EC use as defined, not previously part of that survey, was 11.8%, 6.9% and 1.9% in the three grade groups, respectively. In an unrelated study, high or rising EC use in young people aged 16–19 years in the UK, United States and Canada has not been associated with a decline in smoking, and in Canada, smoking has significantly increased.¹⁴ The always dubious proposition that EC would accurately displace smoking amongst young people without collateral damage¹⁵ can now be filed under 'speculative fallacy'.

Concurrent with the lung disease outbreak and the emerging data for children, action by major regulators is being taken. In the United States, the FDA has determined that JUUL Labs adulterated its products by selling or distributing them as modified-risk tobacco products. Specific concern was voiced about JUUL Labs referring to its products as '99% safer', 'much safer', 'totally safe' and 'a safer alternative'.¹⁶ In that warning letter, dated 9 September 2019, the FDA stated that its concern is 'amplified by the epidemic rate of increase in youth use of ENDS products, including JUUL Labs' products, and evidence that EC products contribute to youth use of, and addiction to, nicotine, to which youth are especially vulnerable'.

On the basis of these events and data showing that fruit and candy flavours are selectively important for EC uptake by young people and never smokers,¹⁷ a range of national and state governments have moved quickly to ban all or selected flavours and/or flavour descriptions. In the Asia-Pacific, India and Timor Leste have recently banned EC completely. In a market increasingly dominated by parties related to major tobacco companies, these decisive actions are most likely when governments can be free from influence by the tobacco industry and its acolytes. Since Dr Chan made her statement in 2015, the World Health Organization (WHO) has been pressured to effectively dilute Article 5.3 of the Framework Convention on Tobacco Control (FCTC), which enshrines policy independence, by widening the pool of stakeholders. Any belief that the "harm reduction" argument, or funding scientists through the Foundation for a Smoke-Free World, could be successfully used as a pretext to create ambiguity around Article 5.3, seems to have been debunked in the latest WHO report on the Global Tobacco Epidemic that described tobacco industry interference as the greatest obstacle to reducing tobacco use and specified Government actions that would protect policies from vested interests.¹⁸

For those who have expressed concerns about the net benefits of EC and recommended precaution, these events bring neither a sense of vindication nor any joy—even if policy steps that we have advocated for are now being taken. Young people are being harmed. Far too many people of a range of ages are becoming seriously ill with lung disease, and some are not surviving their illness. It is a tumultuous time—one for concerted and continued actions.

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